Vitamin D Deficiency in Pediatric Critical Care

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Abstract

Vitamin D deficiency (VDD) is a well-established cause of pediatric bone and muscle disease. In addition, a role has been recognized for vitamin D in the health and stress response of other organs, including the cardiovascular, immune, and respiratory systems. As these organs are central to the development of and recovery from critical illness, VDD has been hypothesized to be a modifiable risk factor for ICU outcome. Over the past 5 years, a growing number of adult and pediatric critical care studies have investigated the prevalence of VDD and its association with illness severity and outcome. The adult studies have recently been synthesized in systematic reviews, with results that convincingly suggest the need for trials to determine whether optimization of vitamin D status improves outcome. In contrast, the pediatric ICU and related literature has not been similarly synthesized. The goal of this review is to describe vitamin D metabolism, known biological mechanisms, potential role in pathophysiology, and summarize the available pediatric intensive care unit (PICU) studies reporting on prevalence of VDD deficiency and its association with outcome. The problems with currently approved supplementation approaches and alternative strategies are discussed, including evidence from available RCTs in adult ICU. Altogether the results suggest that critically ill children are at risk for VDD, and that VDD appears to be associated with a worse clinical course. Clinical trials evaluating novel approaches to testing for and supplementing vitamin D require exploration.

Keywords
- pediatric critical care
- endocrinology
- vitamin D

Introduction

Severe vitamin D deficiency (VDD) is a well-established cause of pediatric disease, including hypocalcemia, skeletal abnormalities, and stunted growth.[1–3] Although severe deficiency is now rare, many adults and children have subclinical VDD that does not manifest classic symptoms. Concern has been expressed about subclinical VDD as research suggests that it could predispose patients to or impair recovery from a variety of neurologic, cardiovascular, respiratory, and immune disorders.[4–6] As these organs are central to the development and recovery from critical illness, VDD has been hypothesized to be a modifiable risk factor for worse outcomes in intensive care unit (ICU).[7]

Over the past 5 years there has been a rapid growth of ICU literature on vitamin D. Dozens of adult studies have convincingly demonstrated associations between VDD and illness severity, patient morbidity, and mortality. This work has culminated in book chapters,[8] narrative reviews,[9–13] systematic reviews,[14–16] pilot clinical trials,[17–22] and a phase III randomized clinical trials (RCT) suggesting safety and clinical efficacy of high-dose supplementation.[23] In contrast, there

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have been relatively few attempts to synthesize the pediatric literature.[24] This review summarizes the pediatric intensive care unit (PICU) literature on VDD, discusses problems with approved supplementation regimens, and presents alternative strategies for evaluation as part of clinical trials.

Vitamin D Deficiency

What Is Vitamin D?

The term *vitamin D* refers to two molecules: ergocalciferol (D2) and cholecalciferol (D3). Both forms can be attained through naturally occurring dietary sources, fortified foods, and pharmaceutical supplements. Of the two, only cholecalciferol can be synthesized in the skin from 7-dehydrocholesterol following ultraviolet (UV) irradiation. Both D2 and D3 are biologically inert, requiring two separate hydroxylations to become active. The initial hydroxylation is performed by liver cytochrome P450 enzymes (25-hydroxylases), producing the prehormone calcidiol or 25-hydroxyvitamin D (25OHD). Calcidiol is the major vitamin D metabolite in the body (nanomolar blood concentrations) and circulates 99% bound to vitamin D–binding protein (VDBP) and albumin. A subsequent nonliver hydroxylation generates the active hormone called *calcitriol* (1,25 dihydroxyvitamin D or 1,25 $(OH)_2D$) (►**Fig. 1**).

Vitamin D Parathyroid Renal Axis

The best understood function of vitamin D is the maintenance of blood and body calcium levels[25] (see ►**Fig. 1**). When blood calcium falls, the parathyroid gland is stimulated and increases parathyroid hormone (PTH) secretion. Higher PTH levels prompt the kidneys to increase hydroxylase activity converting more available calcidiol to active hormone. The active hormone is circulated in the blood to the bone, gut, and kidneys where it binds to vitamin D receptor (VDR) and translocates to the nucleus. The calcitriol:VDR complex interacts with other proteins triggering changes in transcription of hundreds of genes. These changes work to restore calcium homeostasis through increased enteral absorption, decreased renal secretion, and modulation of osteoclast and osteoblast activity.

Nonclassic Functions of Vitamin D

It is now well recognized that dozens of cells outside of the bone, intestine, and kidneys have active VDRs, including myocytes, endothelial cells, white blood cells, pancreatic islets, and skeletal muscle.[26,27] Additional studies have also shown that many cells remote from the kidneys produce α hydroxylases and generate calcitriol from calcidiol for both autocrine and paracrine purposes. Laboratory studies involving both cell lines and animal models have convincingly demonstrated that depletion of vitamin D negatively impacts normal development and stress response. Finally, in addition to altering transcription, it is now evident that vitamin D has nongenomic mechanisms where it can rapidly (within minutes) alter cell functioning through signaling pathways at the plasma membrane (caveolae) or t-tubules.[27–30]

Definition of Vitamin D Status

Calcidiol (25OHD) levels are widely regarded as the best indicator of vitamin D status. Although variability exists, 50 nmol/l is widely used as the threshold to define deficiency, with 25 or 30 nmol/l representing severe deficiency (►**Fig. 2**). Some agencies also recognize an additional state of "insufficiency" with adequate or normal status achieved when levels exceed 75 or 80 nmol/l.[31,32] These thresholds are based on biochemical indicators of axis stress and values below which disease predisposition rises. In brief, when 25OHD falls to 50 nmol/L, maintenance of circulating calcitriol levels requires elevation of serum PTH and increased renal hydroxylase activity.[33,34] As 25OHD falls to 30 nmol/l renal production of calcitriol declines and healthy individuals can develop electrolyte disturbances and clinically evident musculoskeletal pathology.[34–36] These thresholds apply specifically to bone health; the 25OHD concentrations required for optimal nonrenal hydroxylase activity have not been defined.

Explanation of the Potential Role for Vitamin D in ICU Pathophysiology

The biological mechanisms through which VDD may contribute to primary or secondary ICU pathophysiology have been presented in full elsewhere[11,37]; however, a few examples are discussed here.

Hypocalcemia

Hypocalcemia occurs frequently during pediatric critical illness, and both its occurrence and administration of parenteral calcium have been associated with increased morbidity and mortality.[38–41] Normal intra- and extracellular calcium homeostasis is important as it initiates and propagates nerve conduction, muscle contraction, and contributes to signal transduction. In addition to adult critical care studies, pediatric work has shown that patients with low calcium are more likely to have abnormalities of the vitamin D axis, including low 25OHD, hypoparathyroidism, and/or renal dysfunction.[38,39,42]

Immune Dysfunction

Pediatric critical illness is frequently accompanied by an intense inflammatory response.[43,44] VDRs have been identified on all major immune cell types, and current evidence suggests that proper signaling through these receptors is essential for modulating the immune response. For example, vitamin D has been demonstrated to inhibit antigen-induced T-cell proliferation, antagonize the proinflammatory Th1 response, alter gene expression of adhesion factors, and decrease neutrophil adherence and chemotaxis.[45–47] Important functions in innate immunity have also been identified. For example, activation of the VDR is important for transcription and translation of antimicrobial peptides (e.g., cathelicidin).[48–50] Cathelicidin levels have been correlated with both infectious disease outcomes and vitamin D concentrations.[50–52] Pediatric observational studies have linked 25OHD levels and polymorphisms of both VDR and VDBP to various autoimmune and infectious conditions, including RSV, diabetes, and asthma exacerbations.[53–55]

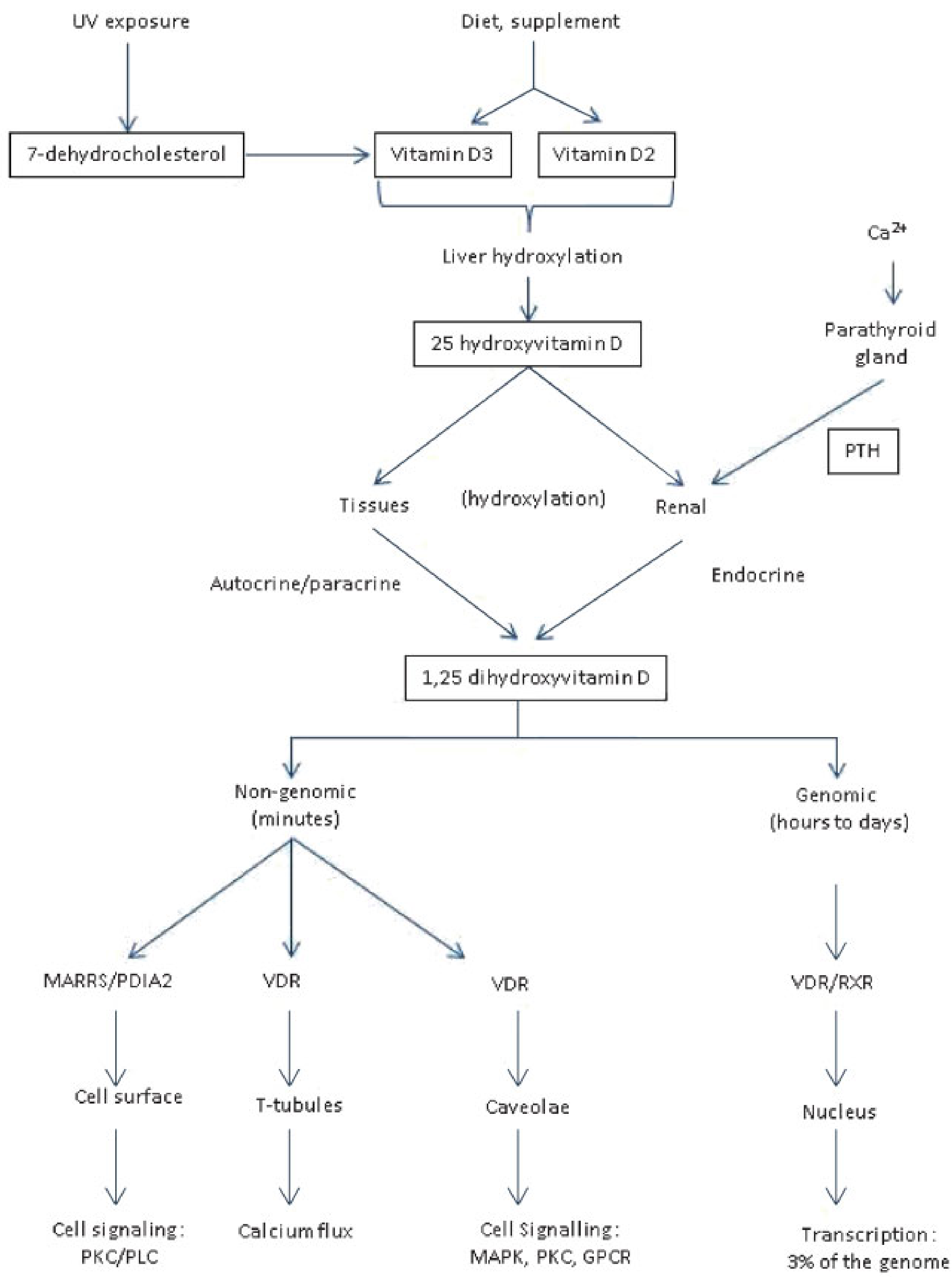

Fig. 1 Metabolism of vitamin D. Vitamin D_3 can be synthesized in human skin following exposure to ultraviolet light. Both vitamins D_3 and D_2 can also be acquired from consumption of specific foods, fortified foods, and pharmaceutical supplements. Both forms are transported to the liver where CYP450 enzymes generate the 25 hydroxyvitamin D metabolite and release it into the circulation. A second hydroxylation is required to produce the active hormone calcitriol. Circulating calcitriol is primarily produced in the kidney by an α hydroxylase that is regulated by parathyroid hormone (positively) and fibroblast growth factor (negatively). Multiple cells also synthesize their own hydroxylase and can locally convert 25OHD for autocrine and paracrine use. Once activated, there are multiple mechanisms through which vitamin D can alter cell function. It is well known that calcitriol binding leads to nuclear translocation of the VDR where it works with transcription factors to upregulate and downregulate transcription of genes. In addition, it has also been established that calcitriol can elicit several rapid nongenomic responses from the plasma membrane (or t-tubules) through binding to the VDR or alternative calcitriol receptors (e.g., MARRS). Abbreviations: Ca^{2+}, ionized calcium; GPCR, G protein coupled receptor; MAPK, MAP kinase; MARRS, membrane-associated rapid-response steroid binding; PDIA3, protein disulfide isomerize family A, member 3; PKC, protein kinase C; PLA, phospholipase A; PLC, phospholipase C; PTH, parathyroid hormone; RXR, retinoid-X receptor; UV, ultraviolet; VDR, vitamin D receptor.

Cardiovascular Dysfunction

Cardiovascular dysfunction is common in PICU, with patients frequently receiving fluid and inotropes to support cardiac output.[56] In addition to indirect effects through calcium, vitamin D influences myocyte structure and function via gene and protein expression.[26] Additional research has shown that myocyte contractility can be favorably altered within minutes by $1,25(OH)_2D$ supplementation, mediated through signal transduction pathways, enzymatic reactions, and ion channels.[28–30] Pediatric clinical studies support these laboratory observations, demonstrating that children with rickets frequently have subclinical cardiac dysfunction along with case reports/series suggesting cardiomyopathy secondary to severe VDD.[57–61] A recent pilot RCT evaluating stable children with heart failure demonstrated improved heart function scores and echocardiographic findings with high-dose vitamin D (2,000 IU/d) when compared with placebo.[62]

Muscle Weakness and Rehabilitation

ICU-acquired weakness is a well-recognized consequence of critical illness, and contributes to mortality, morbidity, worse functional outcomes, and quality of life.[63–66] A significant body of observational research on children and adults has clearly demonstrated that severe VDD can cause muscle pathology and clinically relevant weakness.[67–71] Recently, studies have demonstrated potentially long-lasting effects of high-dose vitamin D on body lean muscle mass in infants and young children.[72,73] Further, a recent RCT evaluating administration of 540,000 IU to critically ill adults demonstrated that patients with 25OHD levels between 30 and 50 nmol/L who received study drug had improved grip strength and physical components of the SF-12.[23]

Prevalence of Vitamin D Deficiency in PICU

Vitamin D Deficiency in PICU

Prior to 2012, little attention was paid to vitamin D status during pediatric critical illness, with only three small studies reporting 25OHD levels on a total of 88 children.[39,74,75] Since 2012 there have been 10 observational studies evaluating vitamin D status in general PICU populations,[76–85] two focused on postoperative congenital heart disease (CHD),[86,87] and a pilot study of high-dose vitamin D in children with burns.[88] The 10 observational PICU studies originate from six countries and evaluate 2,000 children. Almost all studies were single center, collected only one blood sample (at or near admission), and evaluated vitamin D status using total 25OHD. Further, with the exception of Rey and colleagues,[79] all studies defined VDD using the 50 nmol/L threshold. As shown in ►**Fig. 3**, prevalence of VDD ranged from 28 to 84%, suggesting significant risk for VDD in the PICU. Three of the studies also sought to determine whether 25OHD levels were lower in critically ill children compared with other children. Hebbar and colleagues showed statistically lower 25OHD levels compared with a group of unwell children receiving care at the same hospital (99 vs. 46 nmol/L).[81] Similarly, in their investigation of PICU patients with sepsis, Ponnarmeni et al demonstrated significantly lower 25OHD levels compared with healthy controls (49.25 vs. 68.7 nmol/L).[85]

In addition to studies on the general PICU populations, there have been two recent observational studies focused on children with CHD.[86,87] In a secondary analysis, Graham and colleagues reported that 84% of neonates undergoing cardiac surgery had VDD postoperatively. In a prospective Canadian study, mean immediate postoperative vitamin D status was 35 nmol/L (85% VDD). In the pilot RCT of high-dose vitamin D (100 IU/kg) in severe pediatric burn injury, the mean 25OHD concentration was 50 nmol/L.[88]

Change in 25OHD Levels during Hospital Admission

Available PICU literature evaluates VDD at admission but does not address how vitamin D status changes throughout the hospital stay. Only two of the pediatric studies evaluated 25OHD levels at more than one time in the PICU. The Canada multicenter study did not observe differences in group 25OHD levels between days 1 and 2,[76] and the prospective longitudinal study of children undergoing CHD surgery demonstrated that 25OHD levels remained stable over a 48-hour period following separation from cardiopulmonary bypass.[86] Studies from related populations evaluating 25OHD over a longer period provide more useful and concerning findings. In a mixed population of hospitalized children (ward/PICU) Dayal and colleagues observed a significant decline in 25OHD from admission (72 nmol/L) to discharge (49 nmol/L).[89] Similar adult studies by Higgins et al[90] and Yi et al[91] reported a significant decline in 25OHD levels over 10- and 35-day study periods, respectively. The placebo group in a phase III RCT of high-dose vitamin D in critically ill adults found no significant change in 25OHD (mean, 35 nmol/L) over the first 30 days.[23]

Vitamin D Deficiency and Critical Illness

Similar to the general population, reduced consumption of specific foods and inadequate UV exposure (sun avoidance, sunscreen, skin melanin content, high latitude) predisposes many children to preillness VDD. It is also increasingly evident that critical illness and related interventions (surgery, fluids, extracorporeal membrane oxygenation [ECMO], cardiopulmonary bypass, plasma exchange) may significantly reduce vitamin D levels.[86] Disruption of the hepatic, parathyroid and renal organ function (reducing hydroxylation) and greater tissue requirements during catabolism may also reduced 25OHD. Acute changes in 25OHD may be more harmful than chronically low levels as the endocrine axis and individual cells require time to adjust to new steady-state levels.

Association of Vitamin D Status with Illness Severity and Clinical Outcome

Adult ICU Observational Studies

Since 2009, dozens of observational studies have investigated the role of vitamin D in more than 10,000 critically ill adults. Many of these studies estimate concerning VDD rates and report associations with illness severity, organ dysfunction, complications, clinical course, and/or mortality.[7,12–15,19,29–31] In 2014, two systematic reviews synthesized the available literature and calculating an almost twofold greater risk of in-hospital death in VDD.[15,16] Further meta-analysis demonstrated statistically significant differences in sepsis,[15] culture positive infection,[15] and a descriptive analysis suggested an association with increased length of stay.[16] Three large studies, linking hospital laboratory and

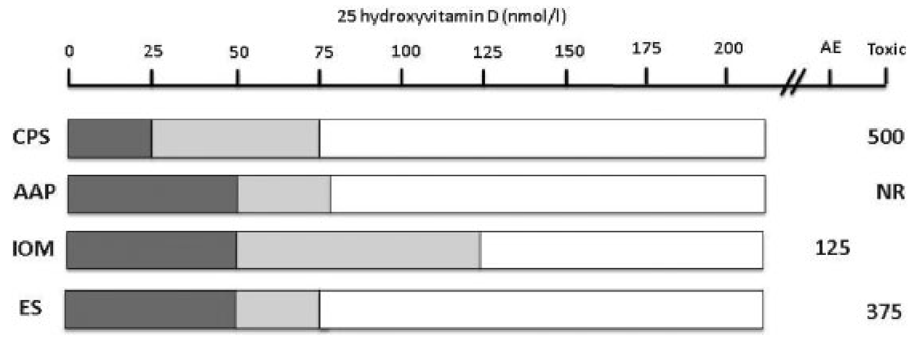

Fig. 2 Example thresholds for vitamin D status. Vitamin D thresholds suggested by various agencies and societies to define vitamin D deficiency (dark bar), vitamin D insufficiency (gray bar), and sufficiency (white bar). The 25 hydroxyvitamin D levels suggested to be associated with adverse events (AE) or toxicity are shown to the right of the bar. Abbreviations: AAP, American Academy of Pediatrics; CPS, Canadian Pediatric Society; ES, Endocrine Society; IOM, Institute of Medicine; NR, not reported.

admission data, determined preillness vitamin D levels to be associated with in-hospital mortality.[92–94] Given the convincing quantity and quality of the observational evidence, multiple adult research groups have proceeded to clinical trials.

PICU Observational Studies

In addition to describing vitamin D status, all the general PICU studies assessed associations between 25OHD and at least one marker of illness severity or clinical outcome. As shown in ►**Table 1**, there is considerable variability in the number and type of measures reported. This lack of consistency, combined with the application of different measurement tools and considerable differences in sample size, makes it challenging to interpret and synthesize the findings. Mortality, the clinical outcome arguably of greatest importance and least subjectivity was reported in six publications. Unfortunately, no individual PICU study was sufficiently powered to investigate an association with mortality. However, it is worth noting that with the exception of the study by Rippel and colleagues,[77] the five remaining studies all reported higher mortality rates in the VDD groups. With the cumulative number of children approaching 2,000, it would be worthwhile combining individual study findings as part of a systematic review and meta-analysis. Of the remaining associations investigated, the two most common included illness severity ($n = 10$) and cardiovascular support ($n = 8$). Overall, an association between illness severity and VDD is strongly suggested as four studies reported statistically significant associations and three studies calculated trends toward statistical significance. Similarly, among the eight studies evaluating cardiovascular outcomes, four reported significantly more cardiovascular support in at least one analysis and two others reported clinically meaningful differences that did not achieve statistical significance. A significant association between 25OHD levels and cardiovascular support was also reported in both studies focused on postoperative CHD patients.[86,87] It is worth commenting on the findings from a few specific studies. First, the lone multicenter study

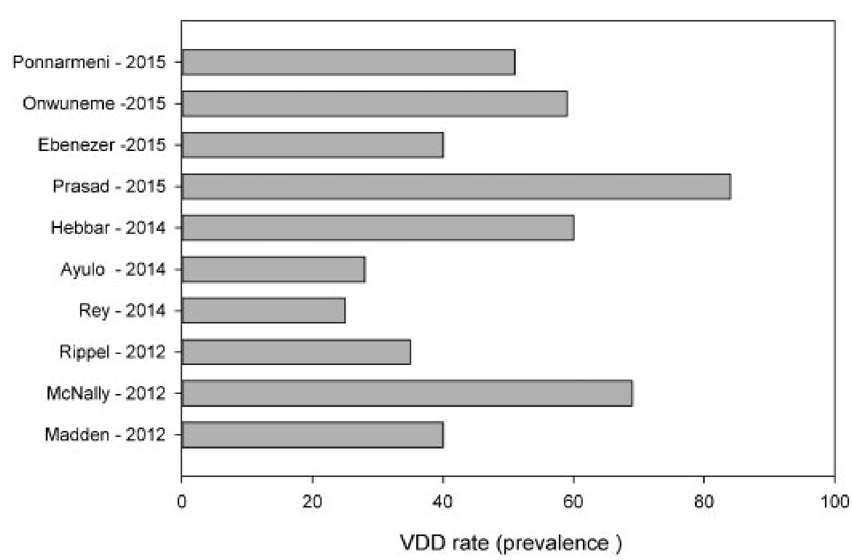

Fig. 3 Prevalence of vitamin D receptor (VDD) in PICU observational studies. This figure shows the prevalence of VDD in the 10 general PICU observational studies. With the exception of Rey and colleagues (37.5 nmol/L), VDD was defined using the 50 nmol/L threshold.

Table 1 Published PICU observational studies reporting on vitamin D status and outcomes

	McNally 2012	Madden 2012	Rippel 2012	Rey 2014	Ayulo 2014	Hebbar 2014	Prasad 2015	Onwuneme 2015	Ebenezer 2015	Ponnarmeni 2015
Sample size	326	511	316	156	216	61	80	120	54	120
Location	Canada	USA	Australia	Spain	USA	USA	India	Ireland	India	India
Age (eligibility)	0–17 y	< 21 y	NR	< 16 y	1–21 y	0–18 y	2 m–12 y	< 12 y	All	1–12 y
Illness severity and outcome measures										
Inotropes/catecholamines	+	+	+	+			+	+	+	+
Calcium/phosphate	+	+	+		+		+		+	+
Fluid requirements	+							+		
Ventilation	+	+	+	+			+	+	+	+
Admission severity score	+	+	+	+	+	+	+	+	+	+
Organ dysfunction						+		+		+
LOS—PICU	+		+	+			+	+	+	+
LOS—hospital			+				+			
Mortality	+		+		+		+		+	+
Coagulopathy/platelets				+			+	+		
Renal failure/dialysis								+		
Hypoglycemia/steroid							+			
Infectious			+			+	+	+	+	+
Inflammatory marker				+				+	+	

Abbreviations: LOS, length of stay; PICU, pediatric intensive care unit.

demonstrated that VDD was associated with a significantly increased length of PICU stay (2 days) after adjusting for important covariates including PRISM (Pediatric Risk of Mortality Score).[76] Second, an Irish study focused on PICU patients with sepsis and the authors reported significantly higher rates of culture proven sepsis in the VDD group.[83] Finally, although the cumulative evidence supports a role for VDD in PICU, it cannot be overlooked that two moderately sized studies failed to find associations with most clinical outcome measures.[77,85] Based on existing work, it would appear that a large multicenter study enrolling a thousand patients, and correcting for important confounders, would be required to further solidify the relationship between 25OHD levels and clinical course. As this observational study would still leave the more important question unanswered, it might be more appropriate to use the resources for a large multicenter interventional.

Approved Vitamin D Supplementation Regimens

Usual Care

Because of the known negative health consequences of VDD, it is recommended that children intake a minimum quantity of vitamin D. The recommended daily allowance (RDA) or adequate intake (AI) suggested by the Institute of Medicine (IOM) and supported by Health Canada are 400 IU for infants and 600 IU for older children.[95] Slightly higher doses have been suggested by the Canadian Pediatric Society (CPS) for infants living in Northern Canada (800 IU).[96] Presently, no standard of care for vitamin D supplementation has been established during or following pediatric critical illness. If ordered at all, a daily dose of vitamin D between 400 and 800 IU is provided enterally or with total parenteral nutrition, but it is well recognized that these doses can take 2 or more months to restore vitamin D status in stable, otherwise healthy children.[73,97] As previously discussed, available evidence on hospitalized and critically ill patients suggests that vitamin D levels generally remain constant or fall over time with usual care.[89,90] As this approach leaves critically ill patients in a VDD state over an extended period, alternative dosing regimens need consideration.

Approved High-Dose Regimens

In addition to RDA, the IOM provides a higher age-specific dose called the tolerable upper intake level (UL), which ranges from 1,000 to 4,000 IU.[95] When given daily, this dose is intended to gradually elevate vitamin D into the high normal range, while safely avoiding toxicity. The UL provided by the IOM was based on evidence from healthy children, and serves as a starting point for research on high-risk populations. A recent systematic review of pediatric clinical trials evaluated dosing in the 1,000 to 4,000 IU range, demonstrating that most patients would not achieve normal levels until after a month of treatment.[98] Further concerning, this systematic review also determined that children who are unwell may have a blunted 25OHD response suggesting that normalization of vitamin D status in deficient critically ill patients using a daily dosing approach may be even slower. A recent pilot RCT evaluating a regimen of 800 IU + 100 IU/kg in pediatric burn patients confirmed these concerns showing that half of the patients remained VDD at the projected midpoint of their hospital admission.[88] Altogether, it appears that approved high-dose daily regimens will not restore vitamin D status in a time frame beneficial for the critically ill child.

Alternative Vitamin D Supplementation Strategies

Loading Dose Vitamin D (Stoss Therapy)

The supplementation strategy most appropriate for the ICU setting is loading dose (or Stoss therapy) where 40,000 to 600,000 IU are provided as single or divided doses. A recent systematic review sought to understand 25OHD response to loading dose therapy in children.[98] Although dozens of studies administering loading dose therapy were identified, none included critically ill children. Evaluation of the change in levels of 25OHD demonstrated that vitamin D levels can be normalized within 48 hours, but that weight-based dosing was necessary to avoid both under- and overdosing. Ultimately, 10,000 IU/kg was proposed as the dose for consideration in future trials.

Trials of High-Dose Vitamin D in Related Populations

There is some clinical trial evidence to suggest that loading therapy may improve outcomes in related non-PICU populations. Primary among the evidence is VITdAL-ICU trial, where 540,000 IU (enteral) and placebo were compared in critically ill adults. Although there was no difference in length of stay (primary objective), there was a clinically meaningful difference in mortality (43 vs. 35%, $p = 0.09$).[23] Further subgroup analysis suggested an interaction between outcome and baseline 25(OH)D level, as (1) participants with baseline 25(OH)D under 30 nmol/L had a statistically significant mortality reduction (50 vs. 35%, $p = 0.02$), and (2) participants with baseline 25(OH)D between 30 and 50 nmol/L showing improved grip strength and physical components of the SF-12 questionnaire. Two pediatric studies evaluating loading dose therapy in ill populations have also suggested benefit. First, an RCT of 450 young children presenting with acute lower respiratory tract infection demonstrated that a 100,000-IU enteral dose reduced repeat episodes.[99] Second, a recent systematic review of pediatric clinical trials of vitamin D in asthma demonstrated that high-dose vitamin D supplementation, including a 60,000-IU monthly loading regimen, reduced asthma exacerbations by 50%.[100,101]

Safety of High-Dose Vitamin D

As an inexpensive and simple intervention, it would be understandable for PICUs to consider overlooking the lack of high-quality clinical trial evidence and begin implementation of high-dose therapy. Preventing this are the concerns spawned from case reports, case series, and a small number of clinical trials establishing that inappropriate vitamin D intake, resulting in supraphysiological 25OHD levels, can cause toxicity.[102,103] Vitamin D toxicity is characterized by hypercalcemia or hypercalciuria, with the classic symptoms (lethargy, abdominal pain, anorexia, constipation, polyuria, and nocturia) directly attributable to these abnormalities. With prolonged states of hypercalcemia and hypercalciuria, children are at risk for developing nephrocalcinosis and other renal pathology. However, there is considerable evidence to suggest that loading dose therapy, designed with the goal of achieving normal vitamin D levels, will be safe. First, studies in healthy children receiving regimens approximating the UL did not demonstrate toxicity with cumulative dosing approximating 10,000 IU/kg.[73,97,104] Second, a review of pediatric nephrocalcinosis studies identified that cases attributed to vitamin D occur in the context of one or more doses of greater than 600,000 IU administered to healthy children or those with genetic abnormalities of VDR.[105–109] Third, an adverse event analysis performed as part of a systematic review of high-dose pediatric trials did not find evidence of toxicity until dosing exceeded 400,000 IU. Fourth, the VITdAL-ICU study did not demonstrate increased hypercalcemia, hypercalciuria, or nephrocalcinosis in the group of vitamin D–deficient critically ill adults that received 540,000 IU.[23] Fifth, pediatric case reports and case series of clinical and subclinical cardiac dysfunction secondary to VDD describe improvements in patient status with both gradual and rapid restoration of vitamin D levels.[57–61,110] Finally, pediatric RCTs evaluating loading dose therapy in healthy and stable unwell pediatric populations (e.g., pneumonia, asthma) have not suggested safety concerns.[99–101,111] Altogether, these findings strongly suggest that rapid normalization of vitamin D status in critically ill children could have more benefit than harm, but further study is necessary to confirm this.

Controversies and Knowledge Gaps

Are There Better Markers for Vitamin D Status for ICU?

Given the high incidence of hepatic, renal, and parathyroid organ dysfunction, it has been suggested that calcitriol might represent a superior marker of vitamin D status in critically ill patients. Two adult studies have been published to date evaluating this question, with neither showing calcitriol to be superior or additive to calcidiol in the relationship with illness severity or clinical outcome.[112,113] A large pediatric study published in 2015 further demonstrated that although associations with interventions and clinical course were evident, they disappeared once 25OHD was considered.[114] More recently, groups have suggested that bioavailable 25OHD might be a better measure, given alterations in VDBP and albumin levels during critical illness. The limited adult and pediatric work in this area have not demonstrated total 25OHD to be inferior,[112,115] but further study is warranted.

Uncertainty Surrounding the Best Dosing Regimen

To date, seven pilot and one phase III trials have been published in various adult ICU settings (►**Table 2**). With the exception of the pilot performed prior to the phase III VITdAL-ICU, none of studies used the same combination of

Table 2 Vitamin D dosing regimens considered to date as part of clinical trials in ICU

	Population	*n*	Metabolite	Dose	Frequency	Route	Usual care arm	Comment
Pediatric—pilot								
Gottschlish, 2015	Burns	18	Ergocalciferol	100 IU/kg	Daily	PO	Yes	
Gottschlish, 2015	Burns	15	Cholecalciferol	100 IU/kg	Daily	PO	Yes	
Adult—pilot								
Ingels, 2010	General	11	Calcidiol	8,000 IU load, 600 IU/d	10 d	IV	Yes	Abstract only
Mata-Granados, 2010	Sepsis	11	Calcidiol	60,000 IU	Days: 0, 4	PO	Yes	Non-RCT
Mata-Granados, 2010	Sepsis	10	Calcitriol	2.0 mcg	Days: 0, 2, 4, 6	IV	Yes	
Amrein, 2011	General, VDD	10	Cholecalciferol	540,000 IU	Once	PO	Yes	
Leaf, 2014	Severe sepsis	36	Calcitriol	2.0 µg	Once	IV	Yes	
Nair, 2015	Sepsis/SIRS	25	Cholecalciferol	150,000 IU	Once	IM	No	
Nair, 2015	Sepsis/SIRS	25	Cholecalciferol	300,000 IU	Once	IM	No	
Dickerson, 2015	Trauma	16	Ergocalciferol	50,000 IU	Once weekly	PO	No	
Dickerson, 2015	Trauma	18	Ergocalciferol	50,000 IU	Twice weekly	PO	No	
Dickerson, 2015	Trauma	31	Ergocalciferol	50,000 IU	Thrice weekly	PO	No	
Rousseau, 2015	Burn	13	Cholecalciferol	200,000 IU	Q3m	IM	Yes	
Amrein, 2014	General	249	Cholecalciferol	540,000 IU then 90,000 IU	Once	Once + per month	Yes	Phase III RCT

Abbreviations: ICU, intensive care unit; IM, intramuscular; IV, intravenous; PO, oral; RCT, randomized clinical trial; SIRS, systemic inflammatory response syndrome; VDD, vitamin D deficiency.

metabolite, dose, frequency, and route. Demonstrating the variability, the metabolites selected in nonplacebo arms included cholecalciferol ($n = 5$), ergocalciferol ($n = 3$), calcidiol ($n = 2$), and calcitriol ($n = 2$). Within the D3 and D2 arms, there were five doses (50,000–540,000 IU) and four frequency options. Importantly, roughly half of the arms utilized intramuscular administration, which has the disadvantage of a longer time to reach peak effect and lower final 25OHD concentration. Although calcidiol is a reasonable option for supplementation, there are valid arguments against the use of calcitriol, the active hormone: (1) increased expense relative to cholecalciferol, (2) knowledge that calcitriol levels do not correlate better with clinical outcome, and (3) observations that loading therapy with D3 or 25OHD results in a rapid rise in calcitriol (two to three fold). Finally, the suggestive results of the VITdAL-ICU trial support further evaluation of enteral loading dose cholecalciferol, but given that many ICU patients cannot receive enteral medications for prolonged periods, it would be reasonable to also explore an IV preparation of cholecalciferol or 25OHD.

Potential Impact and Next Steps

Critical illness occurs in millions of children worldwide every year. In addition to death, these children are at risk for significant morbidity due to organ dysfunction, prolonged periods of rehabilitation, and chronic disease. Given the potential importance of vitamin D to the health and stress response of multiple organ systems, the high VDD rate reported in many ICUs should be of concern. Cumulative observational and clinical trial data suggest that rapid normalization of vitamin D status could represent a simple, inexpensive, and safe means of improving outcomes and reducing health care spending. Unfortunately many of the approved daily dosing regimens for vitamin D can require months to restore levels. Loading therapy represents a more appropriate approach for restoring vitamin D status in critically ill children. Unfortunately, there have been no studies of loading therapy in the PICU setting. Consequently, despite significant literature suggesting VDD to be a modifiable risk factor in critical illness, there is no robust evidence to inform us on how to rapidly normalize levels or the true benefits or risks. RCTs including dose-evaluation pilots and phase III RCTs will be required.

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Conflict of interest
None.

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